Desmosome

Biochemical Characterization of the Desmosome

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Before 1974, the importance of desmosomes in intercellular adhesion was mere speculation based on the ultrastructural likeness of these organelles to cellular "spot welds." The first biochemical isolation of desmosomes, described by Skerrow and Matoltsy (1974a, 1974b), is clearly a milestone that marks a shift from the morphologic studies published before this time, and an emergence of studies reporting expression cloning, cDNA sequencing, molecular characterization and functional analysis of desmosome components. More than 30 years after their isolation technique was developed, it is now apparent that this original hypothesis was indeed accurate, and moreover that desmosomes may play additional roles in tissue morphogenesis that transcend their adhesive functions.

Desmosomes are highly insoluble structures resistant to usual homogenization techniques used for cell fractionation (i.e., hypotonic swelling or physical shearing). Yet, more stringent techniques such as the use of alkali or urea dissolve the structures without maintaining native desmosome organization or protein–protein interactions. In 1974, Skerrow and Matoltsy reported that by using citric acid–sodium citrate buffer to solubilize bovine epidermis and enrich epidermal filaments, they could overcome these limitations and obtain extracts while maintaining desmosome structure (Skerrow and Matoltsy, 1974a). Following solubilization, they used sucrose density gradient centrifugation to separate cell debris, organelles and membrane fragments, and found a fraction that contained many intact desmosomes. In this preparation, larger intermediate filament (IF) bundles were solubilized, but desmosomes, desmosome-associated IFs and most membrane structures were preserved, resulting in a desmosome-enriched preparation that allowed further biochemical characterization. With this technique, Skerrow and Matoltsy were able to separate the desmosome components by SDS-PAGE and showed that several proteins were glycoproteins. They characterized the chemical nature of the desmosome components by measuring the proportions of proteins, carbohydrates and lipids, nonpolar amino-acid content and sialic acid content. On measuring low levels of sialic acid, they correctly deduced that intercellular adhesion is not likely to be attributable to carbohydrate interactions but to other types of interactions between the glycoproteins, contradicting a previous hypothesis on the mechanism of calcium-dependent desmosomal adhesion.

Skerrow and Matoltsy's work was followed by a series of studies from the Franke and Steinberg laboratories, characterizing and purifying desmosome components. Steinberg and colleagues further enriched the glycosylated transmembrane protein component in 1981 with modifications to Skerrow and Matoltsy's isolation technique (Gorbsky and Steinberg, 1981). Using monoclonal antibodies and proteolytic peptide mapping, they began to compare the sequence homology and carbohydrate composition between desmosome glycoproteins in 1983 (Cohen *et al.*, 1983) and began to isolate cytoplasmic plaque proteins in 1985 (Gorbsky *et al.*, 1985).

Werner Franke and colleagues took an inside-out approach and, in 1978, developed a desmosome isolation technique to enrich for IF cytoskeletons and studied the components and characteristics of IF–desmosome plaque complexes (Drochmans *et al.*, 1978). In 1981 and 1983, Franke and colleagues made critical biochemical and immunochemical characterizations of the IF-binding protein desmoplakin (Franke *et al.*, 1981; Mueller and Franke, 1983) and other desmosome plaque proteins (Franke *et al.*, 1983). Franke and colleagues have since made the major contribution towards the discovery and initial characterization of nearly all desmosome plaque proteins known to date. Franke's early work on IF–plaque interactions provided the focus for subsequent studies demonstrating that anchoring of the IF cytoskeleton into the desmosomal plaque is essential for strengthening and maintaining desmosomal intercellular adhesion.

While characterization of the chemical nature of desmosome proteins was being performed, Pam Cowin, David Garrod and colleagues made important observations regarding the biological significance of desmosomes. Cowin and Garrod generated specific antibodies against several desmosome components and used these for immunolocalization and immunoreactivity of desmosome preparations and tissue sections (Cowin and Garrod, 1983; Cowin *et al.*, 1984). They demonstrated that antibodies raised against epithelial desmosomes displayed cross-reactivity between tissues and species, and observed that the distribution of desmosome components was similar

in different tissues and between different vertebrate species. These observations highlight the importance of desmosomes as organelles whose structure and therefore function are highly conserved throughout vertebrate evolution.

The groups mentioned here represent just a few among many others who have made significant contributions to the characterization of the structure and function of the desmosome. The biochemical tools developed by these pioneers constructed the foundation on which all subsequent desmosome researchers build.

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